ORIGINAL RESEARCH

Clinical and Radiographic Evaluation of Calcium Phosphate-Poly(lactide-co-glycolide) Graft in Regeneration of Intrabony Defects: Randomized Control Trial

Moitri Ojha[1], Deepika Pawar Chandrashekara Rao[2], Vishakante Gowda[3]

Abstract

Aim: This study aims to evaluate the efficacy of calcium phosphate-poly(lactide-co-glycolide) composite graft in the regeneration of intrabony defects in chronic periodontitis patients over a period of 12 months.

Materials and methods: A total of 11 systemically healthy chronic periodontitis patients with 22 graftable sites were treated with calcium phosphate cement (CPC) bone graft (control group) and CPC-poly(lactic-co-glycolic acid)(PLGA) composite (test group) after flap reflection and debridement. Clinical parameters such as probing pocket depth (PPD) and clinical attachment level (CAL) were recorded at baseline and 3, 6, 9, and 12 months. Bone probing depth (BPD) and radiographic parameters such as defect depth (DD), changes in alveolar crest level (ALR), defect depth reduction (DDR), and percentage in defect depth reduction (PDDR) were calculated at baseline, and 6 and 12 months. The data were recorded and statistically analyzed.

Results: On intragroup comparison, there was a significant improvement in all the parameters over a period of 1 year (clinically and radiographically). However, there was no statistically significant difference between the two groups in any of the parameters though there was a slightly higher bone fill noted in the test group.

Conclusion: Even though the CPC-PLGA composite bone graft showed a slight improvement in clinical and radiographic parameters as compared to the CPC graft, it was not statistically significant.

Clinical significance: A major drawback of Calcium Phosphate cements as bone grafts is their poor degradability. The PLGA microspheres degrade to expose macropores and interconnected pores in the graft substrate which in turn would promote the ingrowth of osteoblasts. Also, this composite graft is mouldable, and resorbable and has been shown to snugly fit into the defects making them a suitable scaffold material.

Keywords: Bone regeneration, Calcium phosphate cement, Chronic Periodontitis, Composite bone graft, Intrabony defects, Poly(lactide-co-glycolide) microspheres.

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Introduction

Periodontitis is a complex multifactorial disease, some with its basis in genetics, some caused by epigenetic influences, and others that are modifiable.[1] The most important feature of periodontitis is alveolar bone loss and its prevention is essential for the success of periodontal therapy.[2] Regenerative periodontal surgery proposes to re-establish periodontal tissues lost due to the disease process.[3,4] The most common form of regenerative therapy today is bone grafting which usually restores all types of periodontal supporting tissue.[5]

Calcium phosphate biomaterials are the largest group of artificial bone substitutes and are well known in the medical world for treating osseous defects and coating metal alloys for prostheses.[6] In dentistry, these have been extensively used as prefabricated blocks or granules. It is difficult to shape prefabricated blocks while dimensional stability for granules is poor and tends to drift into the surrounding tissue. Several researches have been conducted to modify the properties of this biomaterial alone or combine them with other regenerative materials which are otherwise called composite bone grafts. Nanobone (hydroxyapatite in combination with silicon dioxide) and Fortoss Vital (β-tricalcium phosphate with calcium sulfate) are some well-known commercially available composite bone grafts. Another material that has shown improved results is the biodegradable polymer-poly(lactic-co-glycolic acid) (PLGA) which has been incorporated into calcium phosphate cement in a few clinical trials.[7] Hence, the purpose of this study is to assess the regenerative capacity of calcium phosphate-poly(lactide-co-glycolide) composite graft regarding the clinical and radiographical parameters over a period of 12 months.

Poly D,L-lactic-*co*-glycolic acid or PLGA[8] is hydrolytically unstable and degrades into lactic and glycolic acid, both of which

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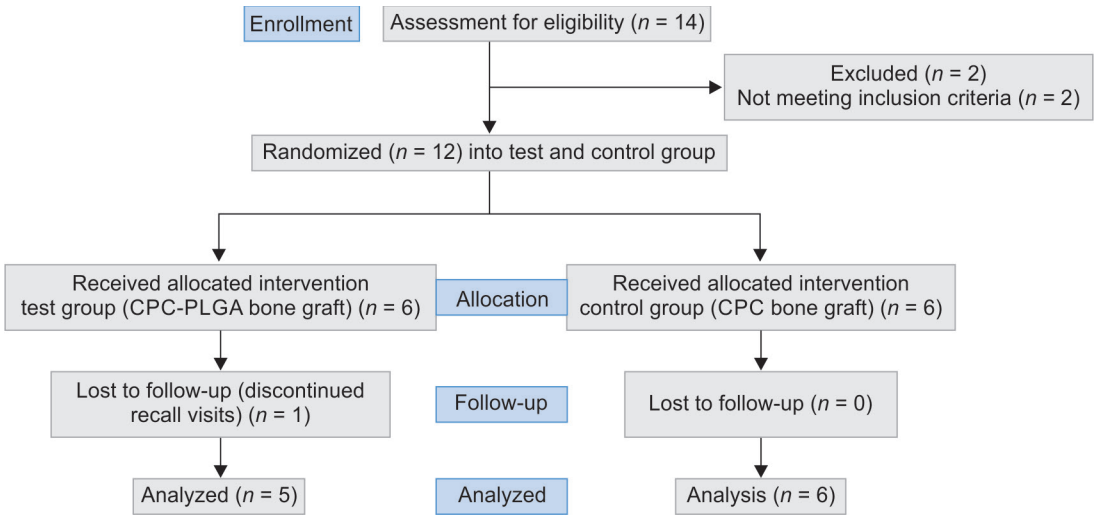
Conflict of interest: None

Flowchart 1: Consort chart



are natural byproducts in numerous metabolic pathways of our body and are eliminated by the kidney. Hence, there is minimal toxicity while using this product.[9,10] Therefore, a new indigenous graft, namely, calcium phosphate-poly(lactide-co-glycolide) composite was fabricated with PLGA microspheres incorporated. On *in vivo* implantation, these polymer microspheres degrade to expose macropores and interconnected pores in the graft substrate which in turn would promote the ingrowth of osteoblasts. The strengthening of graft from this bony ingrowth and deposition of new bone should offset the weakening of graft due to polymer degradation.[10] Also, this composite graft is mouldable, and resorbable and has been shown to snugly fit into the defects.

The purpose of this study is to assess and compare the effectiveness of calcium phosphate-poly (lactide-co-glycolide) composite graft to calcium phosphate cement by analyzing the improvement in clinical parameters and detecting the amount of bone fill over a period of 12 months. No publication up to the author's knowledge is available concerning calcium phosphate-PLGA composite graft in chronic periodontitis patients where both clinical and radiographic parameters were evaluated.

Hence, this study will evaluate the difference in the efficacy of calcium phosphate cement (CPC) graft and calcium phosphate-poly (lactide-co-glycolide) composite (CPC-PLGA composite graft) in the intrabony defects regeneration.

Materials and Methods

The present study was conducted between April 2020 and February 2022 in the Department of Periodontology, JSS Dental College & Hospital, Mysuru, Karnataka, India. This was a double-blinded, parallel-arm randomized controlled clinical trial. The Institutional Review Board approved the protocols for the present study (JSSDCH IEC Research Protocol No. 46/2019) and is also registered in CTRI (CTRI/2020/11/028807). A prior written informed consent was obtained from all the participants involved in the study. They were informed verbally and in writing of the advantages and disadvantages of participating in the study. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity. Based on the level of significance, 0.05; a clinically significant difference (*d*), 2; power, 0.80, and the sample size (*n*) were calculated using the formula,

$$n = 2\frac{\{(Z_{\alpha/2} + Z_{\beta})S\}^2}{d^2}$$

. Hence, a sample size of 12 was determined with 24 graftable sites (12 in each group).

The inclusion criteria of the trial were systemically healthy male and female patients whose ages ranged between 35–55 years of age, patients who had a minimum of two intrabony pockets that measured ≥6 mm, patients who demonstrated vertical/angular bone loss in the radiographs and those who gave their consent and were ready for subsequent follow-ups. Patients on antibiotic therapy or those who had undergone periodontal surgery in the previous 6 months, pregnant/lactating women, smokers, or those who were medically compromised and were under therapeutic medications were excluded from the study. Twelve patients were randomly divided into two groups as follows: Test group and control group following the computer allocation method. One patient having two sites from the test group was lost to follow-up. Therefore, the sample size was re-calculated and finally, the intervention was done on 11 patients (8 females and 3 males) with 22 sites (12 control and 10 test sites) (Flowchart 1).

Calcium phosphate graft was used in the control sites whereas CPC-PLGA composite graft was grafted in the test sites. The aforementioned grafts were formulated at JSS College of Pharmacy, Mysuru, Karnataka, India.

Tetracalcium phosphate (TCP) was obtained by heating an equimolar mixture of calcium carbonate and anhydrous dicalcium phosphate; both materials were received from Lobo Chemie Pvt Ltd. An equimolar ratio of this grounded TCP (20–72.9% mass fraction) and anhydrous dicalcium phosphate (CaHPO4, 27.1% mass fraction) were mixed in a blender. Also, 0.25 gm of this prepared powder was spatulated with 63 µL of distilled water for half a minute. The obtained CPC powder was incubated overnight at a temperature of 37°C and 100% relative humidity (Fig. 1A). This was supposed to be used in the control sites.

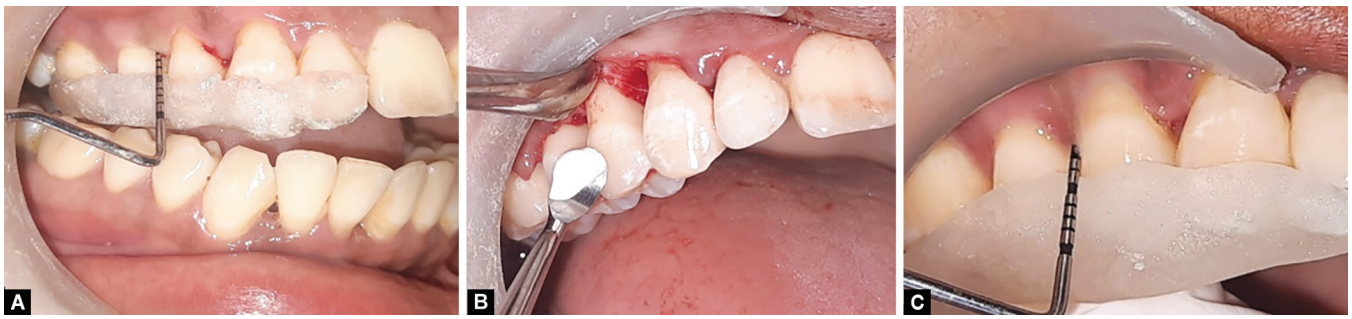
Poly(lactic-co-glycolic acid) copolymer was obtained with a lactide to glycolide molar ratio of 1 (50:50), from Nomisma Healthcare Pvt Ltd, Gujarat, India. To fabricate the microspheres, the solvent evaporation method was adopted. About 20 mL of dichloromethane was used to dissolve 4 gm of PLGA. To this, 1.61 of 1% polyvinyl alcohol was added. Stirring of this solution

was carried out in a hood at 375 rpm for four and a half hours. Solvent evaporation of the solution was done followed by liquid decantation. Using 250 mL of water, the microspheres were washed and cryoprecipitated. With the help of sieves, microspheres (0.18–0.36 mm diameter) were separated and stored at –20°C in the Biochemistry department (Fig. 1B). About 0.15 gm of CPC powder was added to 0.1 gm of PLGA microspheres along with 63 µL of distilled water. This was spatulated for half a minute to obtain CPC-PLGA composite graft. This graft was to be used in the test sites. Both the grafts were placed in separate vials for further use.

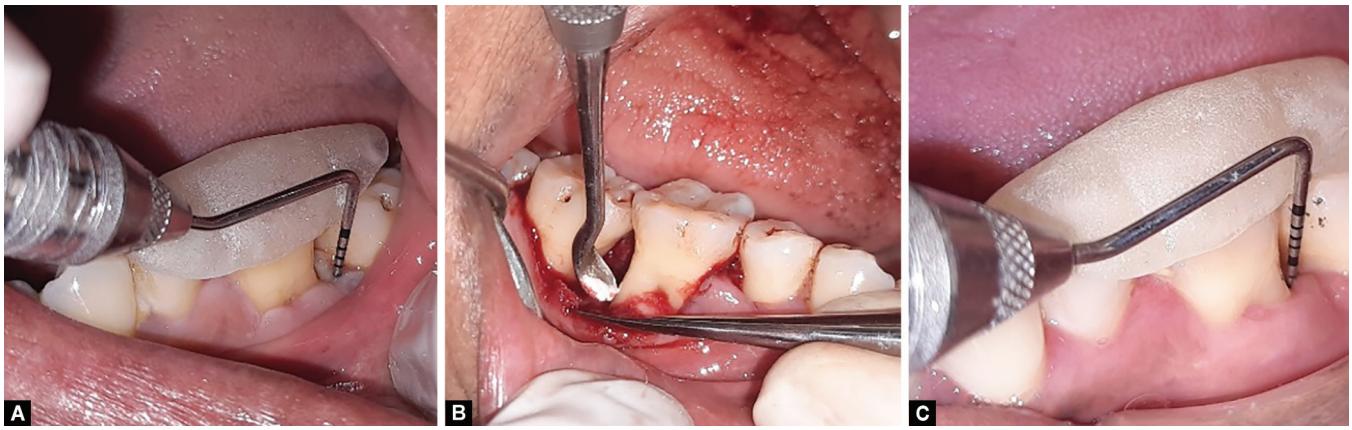
Figs 1A and B: (A) The prepared calcium phosphate cement graft for the control group; (B) The prepared polymer microspheres

Using a gamma chamber, these grafts were exposed to Co-60 gamma radiation (total doses: 25–27 kGy; dose rate of 9.0 kGy/hour). The sterilization procedure was accomplished in Microtrol Sterilization Services Pvt Ltd., Bengaluru, Karnataka, India. The obtained grafts were then sent for scanning electron microscopy (SEM) and X-ray diffraction (XRD) analysis at SJCE, Mysuru, Karnataka, India. Scanning electron microscopy was done to assess the surface morphology of the prepared grafts at an accelerated voltage of 15 kV and a magnification of 1.00, 3.00, 5.00, 10.00, and 20.00 KX. A working distance of 12.5 mm was used. An XRD analysis was performed using 30 kV and 20 Ma to examine the crystallography of the grafts.

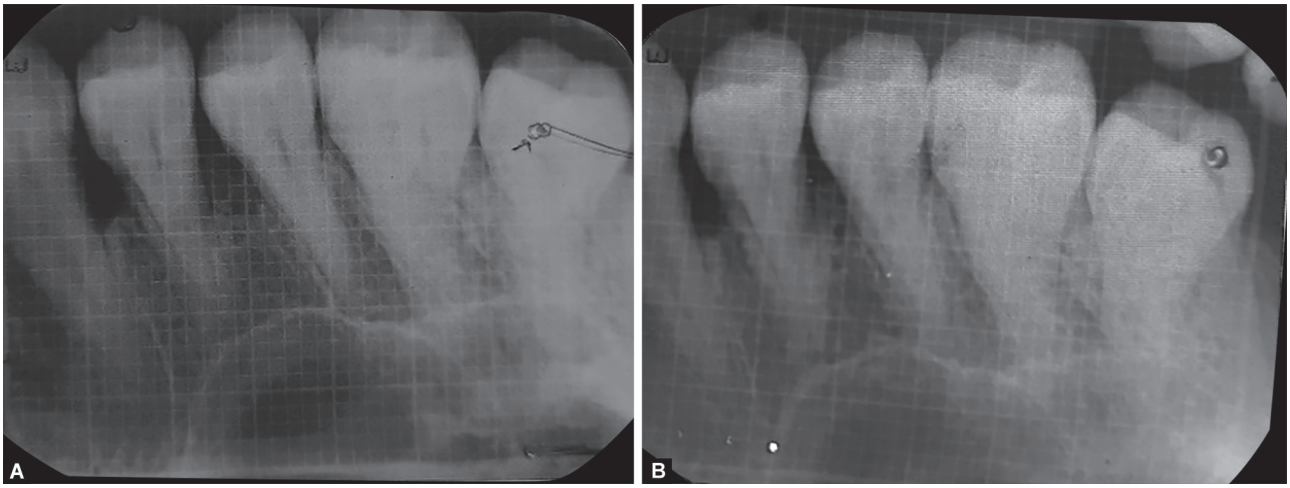
By purposive sampling, 14 patients were chosen to have two or more intrabony defects. Following an initial examination, full-mouth indices were recorded at baseline, 3, 6, 9, and 12 months [plaque index (PI), gingival index (GI), bleeding index (BI), probing pocket depth (PPD), and clinical attachment levels (CALs)]. Phase-1 therapy comprising of SRP was performed under local anesthesia and oral hygiene instructions were given to them. Re-evaluation was done after a period of 6 weeks and two patients who did not maintain oral hygiene were excluded from the study. The selected patients were then scheduled for surgery and full-mouth indices were recorded again. Site-specific parameters (PPD and CAL) were recorded at baseline, 3, 6, 9, and 12 months using a graduated periodontal probe [universal curette-15 (UNC-15) periodontal probe] and standardized customized acrylic stents (Figs 2 and 3). Bone



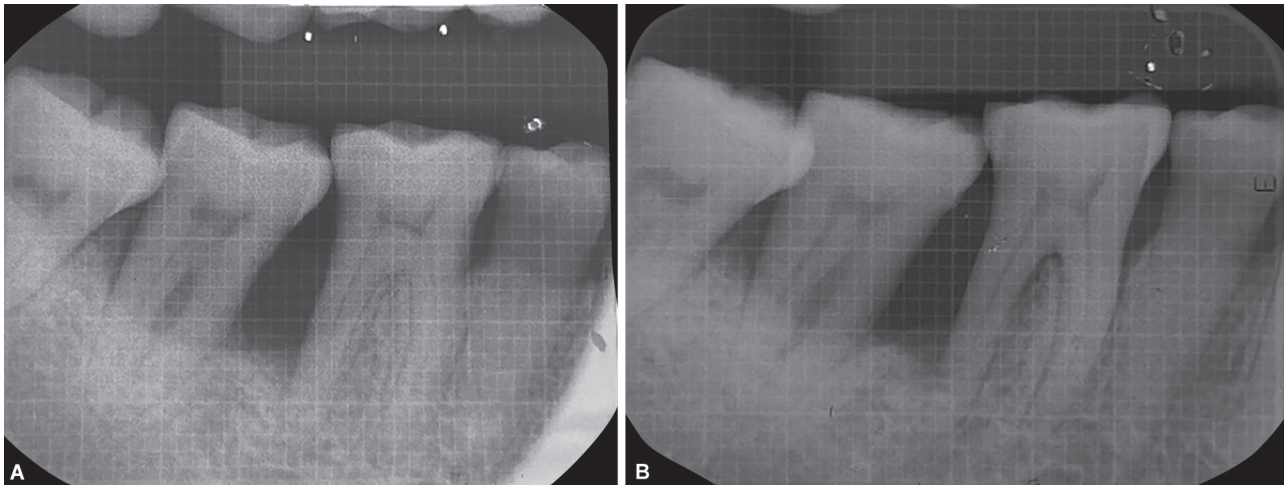
Figs 2A to C: (A) Depicting PPD at baseline; (B) Demonstrating placement of CPC-PLGA bone graft (test group) in the intrabony defect; (C) Showing postoperative PPD after 1 year



Figs 3A to C: Depicting PPD at baseline; (B) Demonstrating placement of CPC bone graft (control group) in the intrabony defect; (C) Showing postoperative PPD after 1 year



Figs 4A and B: (A) Preoperative radiograph of test group at baseline; (B) Postoperative radiograph of test group after 1 year



Figs 5A and B: (A) Preoperative radiograph of control group at baseline; (B) Postoperative radiograph of control group after 1 year

probing depth (BPD) and radiographic parameters [defect depth (DD), changes in alveolar crest level, defect depth reduction (DDR), and percentage in defect depth reduction (PDDR)] were assessed at baseline (Figs 4A and 5A), 6 and 12 months. For radiographic evaluation, conventional intraoral periapical radiographs (IOPAR) with an X-ray mesh gauge (grid-measuring 1 × 1 mm) were used. The following parameters were measured:

PPD = (FRP to BOP) – (FRP to GM)
CAL = (FRP to BOP) – (FRP to CEJ)
BPD = (FRP to BPD) – (FRP to GM)

where PPD is the probing pocket depth; BOP is the base of the pocket; FRP is the fixed reference point; GM is the gingival margin; CAL is the clinical attachment level; BPD is the bone probing depth, and CEJ is the cementoenamel junction.

The cementoenamel junction (CEJ) was taken as the fixed reference point in the radiograph (FRP_R). The landmarks CEJ, alveolar crest, and base of defect were marked on the radiographic image and the distance from CEJ to BOD and AC were measured.

Defect depth = (FRP_R to BOD) – (FRP_R to AC)
Changes in AC level (ALR) = (FRP_R to AC at baseline) – (FRP_R to AC at recall time interval)
Defect depth reduction = Initial defect depth – DD at recalled time interval
Percentage of DDR = (DDR/baseline DD) × 100

With a No. 12 blade, sulcular incisions were placed both on the buccal and palatal sides. A full-thickness mucoperiosteal flap was raised to access the periodontal defects which were then properly debrided and root planed followed by thorough irrigation. The containable defects were treated with bone grafts. A CPC bone graft was placed in the control sites whereas the test sites were treated with CPC-PLGA composite (Figs 2B and 3B). Flaps were repositioned and secured in place with the help of 3–0 silk sutures. The surgical sites were protected by periodontal dressing (Coe pak). Antibiotics (amoxicillin 500 mg thrice daily for 5 days), analgesics (paracetamol and aceclofenac combination twice daily for 3 days), and 0.2% chlorhexidine (twice daily for 7 days) mouthwash were prescribed. Suture removal was done after 7 days of surgery. Patients were recalled at 3, 6, 9, and 12 months to evaluate clinical and radiographic parameters (Figs 4 and 5).

Statistical Analysis

Data were entered in Microsoft Excel and analyzed using statistical package for the social sciences (SPSS), version 24.0,

Table 1: Demographic data distribution of the groups

	Age	*Test site*	*Control site*
n	11	10	12
Minimum	34	1	1
Maximum	51	5	5
Mean	41.36	2.45	2.22
SD	4.56	1.66	1.11

n, number participants; SD, standard deviation

Table 2: Full-mouth PI, GI, BI, PPD, and CALs among the participants

Parameters	*Timeline*	*Mean ± SD*	*p*
PI	Baseline	1.72 ± 0.54	< 0.001
	3 months	0.68 ± 0.24	
	6 months	0.5 ± 0.19	
	9 months	0.44 ± 0.19	
	12 months	0.39 ± 0.15	
GI	Baseline	1.44 ± 0.59	< 0.001
	3 months	0.56 ± 0.26	
	6 months	0.43 ± 0.21	
	9 months	0.53 ± 0.20	
	12 months	0.33 ± 0.19	
BI	Baseline	26.22 ± 19.72	< 0.001
	3 months	9.02 ± 6.21	
	6 months	6.27 ± 3.67	
	9 months	6.77 ± 3.28	
	12 months	4.64 ± 1.56	
PPD	Baseline	5.06 ± 0.68	< 0.001
	3 months	4.00 ± 0.58	
	6 months	3.39 ± 0.53	
	9 months	2.89 ± 0.66	
	12 months	2.84 ± 0.64	
CAL	Baseline	4.91 ± 0.75	< 0.001
	3 months	3.74 ± 0.74	
	6 months	3.15 ± 0.38	
	9 months	2.59 ± 0.38	
	12 months	2.47 ± 0.46	

BI, bleeding index; CAL, clinical attachment level; GI, gingival index; SD, standard deviation; PI, plaque index; PPD, probing pocket depth

software for Windows (IBM Corporation, USA). The results were averaged (mean ± standard deviation) for continuous data and the number, and percentage for dichotomous data are presented in tables. The normality assumption of the data was tested using Shapiro–Wilk test. If the assumption is not significant then a parametric test was carried out otherwise nonparametric test was carried out.

Results

The intervention was done on 11 patients (8 females and 3 males) with 22 sites (12 control and 10 test sites) and a mean age of 41.36 years (Table 1). As this was a double-blinded study, the patient and the examiner recording the data were blinded.

There was an overall reduction in full-mouth PI (from 1.720 ± 0.54 to 0.39 ± 0.15), GI (from 1.44 ± 0.59 to 0.33 ± 0.189), BI (from 26.22 ± 19.72 to 4.64 ± 1.56), PPD (from 5.06 ± 0.683 to 2.84 ± 0.64), and also there was a gain in CAL (from 4.91 ± 0.75 to 2.47 ± 0.46) over a period of 12 months. The difference was statistically significant when calculated at various time intervals ($p < 0.05$) (Table 2).

Table 3: Site-specific PPD, CAL, BPD defect, depth reduction percentage of DDR, PDDR, and alveolar level of the groups

Parameters	*Time interval*	*Mean ± SD (test group)*	*Mean ± SD (control group)*	*p*
PPD	Baseline	7.6 ± 1.34	7.5 ± 0.55	0.8793
	12 months	3 ± 1.73	2.42 ± 0.49	0.4845
	*p**	< 0.001		
CAL	Baseline	7.4 ± 2.61	6.83 ± 0.98	0.6568
	12 months	3.2 ± 1.43	2.17 ± 0.75	0.3719
	*p**	< 0.001		
BPD	Baseline	8.8 ± 1.52	8.67 ± 0.75	0.8625
	12 months	4.3 ± 1.68	3.5 ± 0.84	0.3579
	*p**	< 0.001		
DDR	Baseline	0	0	–
	12 months	1.6 ± 0.42	1.5 ± 0.16	0.6255
	*p**	< 0.001		
PDDR	Baseline	0	0	–
	12 months	46.1± 6.31	40.03 ± 3.97	0.0948
	*p**	< 0.001		
ALR	Baseline	0	0	–
	12 months	1.35 ± 0.20	3.13 ± 1.00	0.6105
	*p**	< 0.001		

*Statistically significant when $p < 0.00$. ALR, alveolar crest level; BPD, bone probing depth; CAL, clinical attachment level; DDR, defect depth reduction; SD, standard deviation; PDDR, percentage of defect depth reduction; PPD, probing pocket depth

Clinical evaluation of site-specific PPD reduction for the control group was 5.08 ± 0.06 at 12 months and 4.6 ± 0.39 in the test group. The gain in CAL for the control group was 4.66 ± 0.23 at 12 months whereas for the test group, it was 4.2 ± 0.25. Each group showed a statistically significant reduction in PPD and a gain in CAL over a period of 12 months. Between the groups, the results were nonsignificant at any given interval.

The mean reduction in BPD for the test group was 3.5 ± 0.34 at 6 months and 4.5 ± 0.16 at 12 months. The mean reduction in BPD for the control group was 4.09 ± 0.27 at 6 months and 5.17 ± 0.93 at 12 months. There was a statistical improvement in both groups over a period of 12 months. On intergroup comparison, there was no statistical difference.

On radiographic evaluation, changes in alveolar crest level at 12 months for the control group was 3.13 ± 1.00 and for the test group, it was 3.35 ± 0.29. Defect depth reduction in the control group was 1.5 ± 0.16 at 12 months. For the test group, the reduction was 1.6 ± 0.42 at 12 months. For the control group, the PDDR was 22.35% at 6 months and 40.03% at 12 months. For the test group, it was 22.83% at 6 months and 46.10% at 12 months (Table 3). Although there was no significant difference between the two groups, a greater bone fill was observed in the test group

Discussion

Biologic principles supporting "composite grafting" narrate the possibility of gaining an additive effect by combining different regenerative materials.[11] In the present study, PLGA microspheres were incorporated into the CPC matrix to evaluate the regenerative

potential of this composite graft. By the addition of this polymer in CPC, a few problems associated with the latter were overcome such as poor degradation rate of CPC bone graft, limited osteoblasts invasion due to pore size, and lack of mechanical strength.[12] This was a double-blinded, randomized controlled clinical trial in the surgical management of 2 or 3 walled intrabony defects over a period of 12 months. The main concern regarding a split-mouth design is that the analysis tends to become complex. Also, there is difficulty in finding similar sites for the same patients.[13] Hence, two separate groups, namely, the test group and the control group were considered. The duration of this study was 12 months based on a study by Machtei et al.[14] who suggested that a 1-year endpoint should be established as the minimal interval for variables measurements when evaluating bone regeneration for a full assessment of the tissue response to the graft material and also to assess its initial stability.

As per the literature records, no study has been published using calcium phosphate-PLGA composite graft in periodontitis patients where both clinical and radiographic parameters were evaluated.

The primary outcome was to evaluate the bone fill and the secondary outcome was to analyze the clinical parameters.

There was an overall improvement in the gingival and periodontal status of the patients over a period of 12 months which was assessed by calculating full-mouth PI, GI, PPD, and CAL.

There was a significant improvement in the site-specific parameters from baseline to 12 months in both groups. On intergroup comparison, there was no statistical difference between the site-specific parameters.

The present study was in accordance with an *in vivo* study conducted by Stevanović et al.,[15] where biphasic calcium phosphate-PLGA composite graft (test group) was compared with demineralized bovine bone graft (control group) in the regeneration of intrabony defects. The trial was performed on 24 patients with chronic periodontitis. The PI, BI, the position of CEJ, and PPD were recorded preoperatively as well as 6 months after the periodontal surgery. The authors concluded that there was a statistically significant improvement in the pocket depth reduction in the test group than the control group.

Also, the research conducted by Ruhé et al.[16] was in accordance with the current trial where a comparison of preset PLGA/Ca-P cement composite discs of various weight ratios (0/100, 15/85, 30/70, and 50/50) was done. The discs were subsequently implanted in the subcutaneous area and the cranial defects of rats were sacrificed after twelve weeks. Histologically, bone formation appeared most abundant and consistent in the specimen of 30/70 PLGA/Ca-P cement. Histomorphometric evaluation revealed an enhanced defect fill in the 15/85 and 30/70 PLGA/Ca-P cement specimens.

Flichy-Fernández et al.[17] evaluated the response of PLGA coated and noncoated biphasic calcium phosphate particles in 36 patients requiring sinus floor elevation. To assess the changes in bone height after the graft placement, the authors performed a CBCT examination preoperatively and 6 months after the treatment. Also, a bone core biopsy was conducted during the implant placement which was further sent for histological analysis (histomorphometric and immunohistochemical evaluation). Results suggested that although there was no significant difference between the groups for the radiographic parameters, yet osteoblastic activities and microvascularization were more evident in the PLGA-coated calcium phosphate group.[12]

A linear change in the radiographic parameters was observed for the present study over a period of 12 months. There was a statistically significant difference noted from baseline to 12 months in terms of ALR, DDR, and PDDR in both groups. Though there was no significant difference in intergroup comparison, a higher bone fill was observed in the test group.

The present study could not analyze the histologic and histomorphometric comparison of both grafts due to ethical concerns. However, there was an increase in the radiodensities in the defect areas due to intrabony defects resolution. Also, in the current study, a conventional IOPAR was used. Hence, it is advisable for future studies to use advanced radiographic aids that would allow for better evaluation.

Conclusion

Thus, within the boundaries of the present study, sites treated with CPC-PLGA composite bone graft showed the same efficacy in both clinical and radiographic parameters assessed over a period of 12 months though test sites showed a slightly greater reduction in the DD. Hence, further studies are required to confirm the beneficial effects of this composite graft in different proportions. Also, a larger sample size is recommended.

Acknowledgment

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Ethical Approval

The study was approved by the Institutional Ethical Committee meeting which was conducted at JSS Dental College & Hospital, Mysuru, Karnataka, India (No. JSS/ACP/Ethical2012-2013).

Data Availability Statement

The data used in the study are available on request by contacting the corresponding author.

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